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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,088	12/05/2003	Martinus Bernardus Vrouenraets	2344-40	8108

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/980,088	VROUENRAETS ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 November 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-3,5-10 and 12-18*.
   Claim(s) withdrawn from consideration: *11*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Response to the Amendment

The Amendment filed on 11/20/2006 in response to the previous Final Office Action (8/18/2006) is acknowledged, but has not been entered because entrance of the amendment would raise new issues with respect 112 2nd paragraph.

Claims 1-3 and 5-18 are currently pending.

Claim 11 is withdrawn from consideration as being drawn to a separately patentable invention from the claims previously under review.

Claims 1-3, 5-10 and 12-18 are currently pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5 and 18 remain rejected under 35 U.S.C. 102(b) as being anticipated by Mauclaire et al. (US Patent 5,268,371, 1993).

Mauclaire et al. teach derivatives of porphyrins and metalloporphyrins derivative carrying four aromatic substituents each of which carries at least one hydroxyl group which is conjugated to a biologically active molecule via a CH_2COOH linking group (Title and Example 8). With regards to the biologically active molecule, the patent teaches (column 8, lines 66-68 and column 9, lines 33-34) that such biologically active molecules include, but are limited to, antibodies, wherein the antibodies are directed against a cell surface antigen of the cancer cells.

In response to this rejection, Applicants assert that claim 1 has been amended to incorporate the subject matter of claim 2. Thus, Applicants contend that Mauclaire does not anticipate the instant rejection because the Mauclaire does not teach four phenyl groups.

As Applicant's arguments appear to be solely drawn to the amended claims which have not been entered, such arguments have not been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3-4 remain rejected and claims 5-6, 13-15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Latouche et al. (Tetrahedron Letters 1995; 36: 1664-1666, IDS) in combination with Mauclaire et al. (US Patent 5,268,371, 1993).

Latouche et al. disclose a porphyrin derivative lacking an antibody which appears to 100% identical to the instantly claimed ring structure of formula (VIII), wherein the ring is a porphyrin ring having four aromatic phenyl substituted Ar's carrying one or more hydroxyl groups suitably linked via a ether linkage to a carboxyl group, e.g., COOH (compound shown on page 1665). The reference further teaches (page 1665, 1st paragraph, lines 3-5) that radiolabelled metalloporphyrins have significantly improved the efficacy of porphyrins for tumor detection, wherein the method can be improved by associating a radioactive metal complex and an antibody in order to deliver the reagent to a specific target. Moreover, Latouche et al. teach that the specific insertion of the metal in the porphyrin even in the presence of a good copper chelator like bovine albumin allows preliminary coupling of these ortho substituted porphyrins with antibodies before ^{64}Cu insertion (page 1666, lines 13-15).

Latouche et al. does not explicitly teach that the porphyrin derivative having four aromatic phenyl substituted Ar's carrying one or more hydroxyl groups is in turn linked via the COOH group to an antibody directed against a cell surface antigen of cancer or other diseased cells.

Mauclaire et al. teach derivatives of porphyrins and metalloporphyrins conjugated to a biologically active molecule (Title). With regards to the biologically active molecule, the patent teaches (column 8, lines 66-68 and column 9, lines 33-34) that such biologically active molecules include, but are limited to, antibodies, wherein the antibodies are directed against a cell surface antigen of the cancer cells. Specifically, Mauclaire et al. teach (column 5, lines 38-53) that the presence of the COOH group on the porphyrin gives them the property of being covalently bondable to biologically active molecules such as antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Latouche et al. and Mauclaire et al.. One would have been motivated to do so because as taught by both Latouche et al. and Mauclaire et al., porphyrin derivatives coupled to a biologically active molecule have a better affinity due to the presence of said biologically active molecule, e.g. target cell specificity (page 1665, 1st paragraph, lines 3-5 and column 9, lines 28-34 respectively). Thus, one of ordinary skill in the art would have a reasonable expectation that by conjugating an antibody with a porphyrin derivative as taught by Latouche et al. in view of Mauclaire et al., one would achieve a cancer cell specific porphyrin antibody conjugate which may be used for detection and/or treatment of tumor cells.

In response to this rejection, Applicants assert that claims 1 and 18 have been amended to incorporate the subject matter of claim 2, which is not rejected on obviousness grounds over Latouche in combination with Mauclaire. As such, Applicants assert that withdrawl of this obviousness rejection on this ground alone is believed to be in order.

As Applicant's arguments appear to be solely drawn to the amended claims which have not been entered, such arguments have not been considered.

Claims 1-3 remain rejected and claims 5-10, 12-13 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnet et al. (US Patent 4,992,257, 1991, IDS) in combination with Latouche et al. (Tetrahedron Letters 1995; 36: 1664-1666, IDS) and Mauclaire et al. (US Patent 5,268,371, 1993) in view of Westerman et al. (Int. J. Cancer 1998; 76: 842-850).

Bonnet et al. teach (column 8, lines 37-68) dihydro and tetra-hydro porphyrins (referred to as chlorins and bacteriochlorins respectively, column 6, lines 21-24) having four aromatic phenyl substituted rings carrying one or more hydroxyl groups, wherein the hydroxyl groups may be in the

ortho, para or meta position. With regards to the dihydro and tetra-hydro porphyrins, the patent teaches that the dihydro and tetra-hyrdro porphyrins include, but are not limited to, p-THPC, m-THPC, o-THPC and m-THPBC (column 6, Table 2). Bonnet et al. further teach (column 1, line 65 to column 2, line 1) that the compounds can be used as a form of cancer therapy, wherein the compound is administered to locate in the tumor followed by illumination of the tumor with light of a wavelength absorbed by the compound.

Bonnet et al. do not explicitly teach that the dihydro and tetra-hydro porphyrins (referred to as chlorines and bacteriochlorins respectively, column 6, lines 21-24) having four aromatic phenyl substituted rings carrying one or more hydroxyl groups are in turn linked to an antibody against a cell surface antigen of cancer cells. Nor does Bonnet et al. teach that the antibody and porphyrin derivatives are linked via an ether linkage through a COOH group.

The combination of Latouche et al. and Mauclaire et al. teach, as applied to claims 1 and 3-4 above, a porphyrin derivative having four aromatic phenyl substituted Ar's carrying one or more hydroxyl groups linked via a ether carboxyl group, e.g., COOH, to an antibody which binds a surface cell cancer antigen. Moreover, Mauclaire et al. teach (column 5, lines 38-53) that the presence of the COOH group on the porphyrin gives them the property of being covalently bondable to biologically active molecules such as antibodies, while Latouche et al. teach a method of generating the porphyrin derivative having an ether linked COOH group via alkylation of the phenolic hydroxyl by ethyl bromoacetate followed by saponification of the ester group (page 1665, last paragraph).

Westermann et al. teach (page 842, 2nd column, 1st full paragraph) that the major disadvantages of m-THPC phototherapy include, but are limited to, a relatively low tumor selectivity which, in view of the strong photoxic properties, can lead to undesired side effects in adjacent normal tissues. As a way to circumvent this disadvantage, the reference teaches a conjugate comprising the photosensitizer metal-tetrahydroxyphenylchlorin (m-THPC) conjugated to polyethylene glycol which preserves its function of phototherapy and represents an interesting first step in favor of the strategy of conjugating photosensitizing dyes to anti-tumor antibodies (page 849, 2nd column, 2nd paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to specifically target a cancer

cell with m-THPC. One would have been motivated to do so because as taught by Westerman et al., one of the major disadvantages with m-THPC phototherapy is the lower tumor selectivity that leads to undesirable side effects. Thus, one of ordinary skill in the art would have a reasonable expectation that by alkylating the hydroxyl groups of m-THPC followed by saponification in view of Latouche et al., one would achieve a covalently bondable COOH group on m-THPC which can be linked to an antibody for specific tumor localization of m-THPC.

Moreover, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

In response to this rejection, Applicants submit that Bonnett discloses the synthesis of dihydroporphyrins, but makes no mention of or suggestion of the use of monoclonal antibodies. Applicants further submit that Mauclaire is not relevant because it deals with the problem of linking monoclonal antibodies by providing a single phenyl group R2 around the porphyrin ring, the remaining three R1 groups being pyrindyl radicals. Moreover, Applicants assert that Westermann discloses an old method for coupling porphyrins to a polyethylene glycol, but there is no disclosure or suggestion of coupling monoclonal antibodies. In addition, Applicants assert that while Westermann indicates that this observation represents "an interesting first step in favor of the strategy of conjugating photosensitizing dyes to anti-tumor antibodies, this is not a disclosure which would lead one of ordinary skill to the present invention based on the cited art combination.

As Applicant's arguments appear to be solely drawn to the amended claims, which have not been entered, such arguments have not been considered.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mauclaire et al. (US Patent 5,268,371, 1993) in further view of Bendig et al. (WO 92/15683, 1992).

Mauclaire et al. teach, as applied to claims 1, 3, 5 and 18 above, derivatives of porphyrins and metalloporphyrins derivative carrying four aromatic substituents each of which carries at least one hydroxyl group which is conjugated to a biologically active molecule via a CH_2COOH linking group (Title and Example 8). With regards to the biologically active molecule, the patent teaches (column

8, lines 66-68 and column 9, lines 33-34) that such biologically active molecules include, but are limited to, antibodies, wherein the antibodies are directed against a cell surface antigen of the cancer cells. Moreover, the patent teaches that the porphyrin derivatives may be used as diagnostic or therapeutic agents for tumors.

Mauclaire et al. do not explicitly teach that the antibody is mMAb 425.

Bendig et al. teach that murine monoclonal antibody 425 (Mab 425) binds to a polypeptide epitope on the external domain of the human epidermal growth factor receptor and inhibits the binding of epidermal growth factor at both low and high affinity EGFR sites (page 3, lines 7-12). Moreover, Bendig et al. teach that enhanced expression of EGFR is found to occur on malignant tissues from a variety of sources, thus making mAb 425 a useful agent for the diagnosis and therapeutic treatment of human tumors (page 3, lines 12-21).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conjugate mAb 425 to the porphyrin derivatives taught by Mauclaire et al. in view of Bendig's teachings that mAb 425 is a useful agent for the diagnosis and treatment of human tumors due to EGFR's enhanced expression in a variety of tumors. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by conjugating mAb 425 to the porphyrin derivatives, one would achieve a porphyrin:mAb 425 immunoconjugate useful for the treatment or diagnosis of tumors characterized by enhanced EGFR expression.

In response to this rejection, Applicants assert that while Bendig discloses a particular humanized monoclonal antibody, the reference does not disclose or suggest as to why this particular monoclonal antibody should be employed in the porphyrin rings of the present invention.

As Applicant's arguments appear to be solely drawn to the amended claims, which have not been entered, such arguments have not been considered.

Therefore, NO claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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1/3/2007

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